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XENOTRANSPLANTATION

SCIENTIFIC FRONTIERS AND PUBLIC POLICY

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Welcoming Remarks

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I welcome you to this very important meeting and greatly appreciate the significance of the topic that is going to be addressed here. When I was asked to make a few preliminary remarks at this meeting, something in the back of my head prompted me to rummage through my old papers, and there I found something relevant that I had written about 35 years ago. This paper, from which I've taken the quotation below, says it all about the problems we are confronting today with the issues raised by xenotransplantation:

> There is little evidence of forethought on the social impact of the solution to the homograft problem, which seems very near, and may be a prototype for the exercise of responsible power in biological engineering. Nor has the full impact of tissue replacement on the practice of medicine been widely appreciated. For example, many therapeutic regimens are now barred or restricted by the possibility of damage to some organs in the course of therapy. The medical revolution should also encourage some anxieties over its orderly progress. Perhaps these anxieties have been sublimated into unrealistic skepticism of the accomplishment. We must recall that the homograft barrier has preserved the personality of the body. We have not hitherto had to think deeply on the technology and ethics of allocating precious organs for lifesaving transplantations. The potential dehumanizing abuses of a market in human flesh are fully anticipated in imaginative literature; modest proposals have been wryly recorded for the furtherance of international trade. Ultimately we must also reserve some concern for the identification of the person: what is the moral, legal, or psychiatric identity of an artificial chimera?
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> [recommendations]
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> A vigorous eugenic program, not on man, but on some non-human species to produce genetically homogeneous material as sources for spare parts. Apart from touchier issues, the technical problem of overcoming the immune barrier would be immensely simplified if the heterografts came from a genetically constant source, the more so if this could be purposefully bred for this utility. At present the only adequately inbred mammals are small rodents.[1]

The symposium I wrote this for was the first Ciba Foundation symposium to have a policy rather than a technical orientation. In that respect it reflects the reach that the New York Academy of Sciences has made in co-sponsoring this workshop. Most of our conferences are more oriented to the scientific and technical side, but with some concession to policy. The emphasis in this symposium will be somewhat the converse.

As I reconsider the context of the remarks above, the one place where my prophetic vision was absolutely clouded was the expectation that we would have a prompt biochemical solution to the problem of graft rejection. Of all the things I said in my discourse at the time, that was the one that was furthest from the mark.

And even now, 35 years later, we are far from having found satisfactory technical solutions. Our methods of alleviating the problem of graft rejection—and often the graft-versus-host can be just as difficult as the host-versus-graft—are extremely crude and not very selective. They involve more or less global immunosuppression of the host, which can have disastrous consequences. And I have to shed a tear, quite

literally, for one of my dear friends and colleagues who was, in fact, killed by cyclosporin as an attempted remediation for the kidney graft he had received. Such a death is, unfortunately, not a totally rare event.

But we do see some glimmer of hope on the horizon. There is little doubt about the validity of one of the premises of my argument that if we are going to go into xenotransplantation, the task would be greatly simplified if we had genetically homogeneous material as the source of the grafts so that we can direct our energies towards inducing auto-tolerance or whatever specific immunosuppressive measure will be required. So there is a little light at the end of what I won't call a tunnel, for the area of darkness is more like a catacomb.

Another problem I had absolutely not foreseen is the extent to which the use of exotic species for tissue or organ transplants might be a source of new and emerging infections. We had no hint of phenomena like the HIV pandemic nor had we even seen the much more limited but acutely vicious outbreaks of Lassa fever and Marburg fever that brought the realities of the zoonotic source of major human diesase to the forefront of everyone's attention. We didn't even know about the hepatitis A virus at that time. So this issue of zoonotic transmission of disease looms as another one of the complications of using exotic species not rigorously controlled as sources of material.

This problem represents a complication of the use of human transplant material. And by now, as many as 100 cases have been reported of transmission of prion disease to humans by the use of human graft material or human source material in the remediation of growth factor deficiency, among other such uses.

And that does not even address the very substantial number of infections that derive from other sources. And, of course, blood transfusion must be included as a very significant kind of transplantation.

On the other hand, we have to consider the benefits of this new technology, far out as they may be. The prospects for the applicability of routinely available grafts without the horrendous ethical, logistic, and economic problems that are entailed in the current use of human tissue for graft purposes are easy to underestimate. We don't really have an adequate vision of the way in which remedial medicine would be totally transformed if organs could be replaced at will, at fairly low cost, and with a high degree of reliability and a minimum of side effects.

Operations that are now being done, like transplantation of the heart, lung, liver, and kidney absolutely revolutionized the practice of medicine. Now suppose heart replacement were a routine matter, not much different from repairing a broken bone. What questions would this open up in terms of interventional surgery in other areas? It is very difficult to envisage the possible consequences.

The heroic measures involved in the reconstruction of the human body in the face of illness are often limited by the frailty of the heart. Some persons are too old, too feeble, too disorganized in other respects to be good candidates for extremently intrusive procedures. And while such transplantations might indeed be live-saving, they are limited by the constraints posed by the heart.

We have also seen the emergence of many of the social, political, and ethical problems that are begged by, not to use too lurid a term, the marketing of human flesh. This issue has become quite intense, has required very substantial regulation, and has evoked many questions abut the social equities involved. When it comes to

the compensation of potential donors for organs, we are damned if we do and damned if we don't. Enormous stresses in family-related situations occur where altruistic motives are at the fore in the procurement and provision of these sources. By and large the situation is an absolute mess. At the present state of our technology we have little recourse but to go through the kinds of procedures for allocation and regulation of allocation of organs. But quite apart from the biological risks that are entailed in introducing exotic tissue into our own frame, we also have a very complicated series of dilemmas on the social and ethical side. So God bless if we can achieve safe, reliable, and economic xenotransplantation and can afford to cultivate animals to provide spare parts in a way that removes the deep affront to human dignity that may occur when we use human bodies for that purpose.

But other problems exist as well. Even setting aside the issue of using exotic species, with their unknown and unknowable burden of viruses, such as those we've seen with wild monkeys, we find that even some of our closest relatives, the swine, offer us previously unforeseen burdens in terms of retroviruses and other infectious agents.

We must contemplate that our own genome has 400 or 500 copies of different retroviruses that are already integrated with unknown consequences. These from time to time may be reactivated, perhaps even by allotransplant. How daunting it is is to contemplate what might arise from the use of other animal species, no matter how carefully and thoroughly inbred! However, at least there is the prospect that these issues can be faced once and for all when we have gone through the repertoire of the viruses carried in an inbred line of pigs. With modest precautions we can be reasonably confident that we have plumbed the problem. But when wild species are used, and their organs introduced into immunocompromised hosts, which is the built-in circumstance of their use, we are taking terrible risks of evoking new diseases. At the very minimum, even at a limited experimental level, there should be extremely stringent monitoring, surveillance and testing to make sure that we have not invented brand new horrors in our desire to do good.

Our desire to *not* bring forth horror and to *do* good is the real subtext of this symposium. It is very important that there should be thoughtful examination of the ethical and policy issues that surround an equally difficult set of technical issues in achieving success and I wish you all God-speed in your venture.

REFERENCE

1. LEDERBERG, J. 1962. Biological future of man. *In* Man and His Future. G. Wolstenholme, Ed.: 263–273. Ciba Foundation Symposium. London.